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Name (Print/Type)	Michael A. Moore	Centralized Fax No. 703-872-9306	
Signature	Michael A. Moore	*Date*	February 25, 2004

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
PAUL A. SECHRIST

Serial No.: 10/007,853

Filed: November 5, 2001

Attorney Docket No. 106462

CYCLIC CATALYST REGENERATION PROCESS USING ADSORPTION AND DESORPTION ON VENT STREAM

Examiner: Strickland, Jonas N.

Art Unit: 1754

REPLY

Commissioner for Patents
Alexandria, VA 22313-1450

Sir:

In response to the Office action dated September 25, 2003, favorable reconsideration of the subject application is respectfully requested in view of the following remarks.

REMARKS

Claims 1-22 are pending.

Claims 1-4, 18, and 19 are objected to because they recite "selected from the group consisting of". It is believed that these claims are acceptable, since one acceptable form of alternative expression in claims is a Markush group, which recites members as being "selected from the group consisting of ...". MPEP § 2173.05(h) Alternative Limitations, I. Markush Groups. Therefore, it is submitted that these objections should be withdrawn.

Claims 1-22 of the subject application are provisionally rejected under 35 U.S.C. §101 as being unpatentable over claims 1-22 of copending U.S. Application No. 10/010,564 on the grounds that claims 1-22 of the subject application claim the same invention as claims 1-22 of the '564 application. This rejection should be withdrawn because claims 1-22 of the subject application do not claim the same invention as claims 1-22 of the '564 application.

Claim 1 of the subject application recites in (d) forming the regeneration inlet stream from both at least a portion of the desorption effluent stream and a second portion of the regeneration effluent stream, while claim 1 of the '564 application recites in (d) forming the regeneration inlet stream from at least a portion of the desorption effluent stream. The test for same invention is "whether one of the claims being compared could be literally infringed without literally infringing the other. If it could be, the claims cannot define identically the same invention." In re Vogel, 164 U.S.P.Q. 619, 622 (CCPA, 1970). In this case, if the regeneration inlet stream is not formed from a second portion of the regeneration effluent stream, then claim 1 of the '564 application could be literally infringed without literally infringing claim 1 of the subject application, which requires that the regeneration inlet stream be formed from a second portion of the regeneration effluent stream. Therefore, claim 1 of the subject application does not claim the same invention as claim 1 of the '564 application. Accordingly, it is believed that claim 1 of the subject application meets the requirements of 35 U.S.C. §101 and that the rejection of claim 1 of the subject application under 35 U.S.C. §101 should be withdrawn. The rejection of claims 2-15 of the subject application under 35 U.S.C. §101 should be withdrawn for the reason given in support of claim 1 of the subject application because they are dependent on claim 1 of the subject application.

Claim 16 of the subject application recites in (e) forming the regeneration inlet stream from both at least a portion of the desorption effluent stream and a second portion of the regeneration effluent stream, while claim 16 of the '564 application recites in (e) forming the regeneration inlet stream from at least a portion of the desorption effluent stream. If the regeneration inlet stream is not formed from a second portion of the regeneration effluent stream, then claim 16 of the '564 application could be literally infringed without literally infringing claim 16 of the subject application, which requires that the regeneration inlet stream be formed from a second portion of the regeneration effluent stream. Therefore, claim 16 of the subject application does not claim the same invention as claim 16 of the '564 application. Accordingly, it is believed that claim 16 of the subject application meets the requirements of 35 U.S.C. §101 and that the rejection of claim 16 of the subject application under 35 U.S.C. §101 should be withdrawn. The rejection of claims 17-22 of the subject application under 35 U.S.C. §101 should be withdrawn for the reason given in support of claim 16 of the subject application because they are dependent on claim 1 of the subject application.

Claims 1-22 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,965,473 (Sechrist). Claim 1 recites a process comprising contacting a regeneration inlet stream with a catalyst in (a) and contacting a desorption inlet stream with an adsorbent in (c). Sechrist teaches a process in which a regenerant gas contacts catalyst in a catalyst bed in order to regenerate that catalyst and in which the contacting removes chloro-species from the catalyst. Col. 2, lines 1-8, col. 11, line 24 to col. 12, line 59, and col. 20, line 66 to col. 21, line 42. But Sechrist does not teach or suggest a process that comprises both contacting a regeneration inlet stream with a catalyst *and* contacting a desorption inlet stream with an adsorbent. In fact, Sechrist teaches away from using an adsorbent that is separate from the catalyst. Col. 2, line 19 to col. 3, line 18. Therefore, Sechrist does not motivate a person of ordinary skill in the art to contact an adsorbent with a desorption inlet stream. Accordingly, it is believed that claim 1 meets the requirements of 35 U.S.C. §103(a) and that the rejection of claim 1 under 35 U.S.C. §103(a) as being unpatentable over Sechrist should be withdrawn. The rejection of claims 2-15 under 35 U.S.C. §103(a) as being unpatentable over Sechrist should be withdrawn for the reasons given in support of claim 1 since they are dependent on claim 1. Claim 16 recites a process comprising passing a regeneration inlet stream to a catalyst bed containing a catalyst in (b) and passing a desorption inlet stream to a desorption zone containing an adsorbent in (d). The rejection of claims 16 under 35 U.S.C. §103(a) as being unpatentable over Sechrist should be withdrawn for the reasons given in support of claim 1. The rejection of claims 17-22 under 35 U.S.C. §103(a) as being unpatentable over Sechrist should be withdrawn for the reasons given in support of claim 16 since they are dependent on claim 16.

In view of the foregoing remarks, favorable reconsideration of the subject application is respectfully requested.

Respectfully submitted,

UOP LLC

Michael A. Moore

Michael A. Moore
Attorney for Applicant
Reg. No. 41,203

PTO/SB/21 (08-03)
Approved for use through 08/30/2003. OMB 0651-0031
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission: 7

Application Number	10/007,853
Filing Date	11/05/2001
First Named Inventor	Paul A. Sechrist
Art Unit	1754
Examiner Name	Strickland, Jonas N.
Attorney Docket Number	106462

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [x] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [x] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
- [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] After Allowance communication to Technology Center (TC)
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC (Appeal Notice, Brief, Reply Brief)
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please identify below):

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Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Michael A. Moore
Signature	Michael A. Moore
Date	February 25, 2004

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Signature	Michael A. Moore	Date	Feb. 25, 2004

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PTO/SB/17 (10-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 420

Complete if Known	
Application Number	10/007,853
Filing Date	11/05/2001
First Named Inventor	Paul A. Sechrist
Examiner Name	Strickland, Jonas N.
Art Unit	1754
Attorney Docket No.	106462

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☑ Credit card ☐ Money Order ☐ Other ☐ None

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The Director is authorized to: *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) or any underpayment of fee(s)

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below	Fee Paid
Total Claims	-20** =	X	$18	=
Independent Claims	- 3** =	X	$86	=
Multiple Dependent				=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	420
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) 1814 Statutory disclaimer ($110)

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($) 420

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Michael A. Moore	*Registration No. (Attorney/Agent)*	41,203	*Telephone*	847-391-2948
Signature	Michael A. Moore			*Date*	Feb. 25, 2004

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Name (Print/Type)	Michael A. Moore	*Centralized Fax #*	(703) 872-9306
Signature	Michael A. Moore	*Date*	February 25, 2004

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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FEB 25 2004

In re Application of
Paul A. Sechrist

Serial No.: 10/007,853

Filed: 11/05/2001

Attorney Docket No. 106462

CYCLIC CATALYST REGENERATION PROCESS USING ADSORPTION AND DESORPTION ON VENT STREAM

Examiner: Strickland, Jonas N.

Art Unit: 1754

Confirmation No.: 7587

OFFICIAL

Commissioner for Patents
Alexandria, VA 22313-1450

REQUEST FOR EXTENSION OF TIME

Applicant, through their attorney, respectfully requests a two-month extension of time within which to respond to the Office action dated September 25, 2003.

A fee transmittal form, as well as authorization for credit card payment of the fee, are attached.

Respectfully submitted,

UOP LLC

Michael A. Moore
Attorney for Applicant
Reg. No. 41,203

MAM:sb

02/27/2004 AWONDAF1 00000022 10007853

01 FC:1252 420.00 OP

action as well as from about 10 to about 20 weight-% of microcrystalline cellulose (Avicel®) and other pharmaceutically acceptable adjuvants. In the cited prior art literature no mention is made of the use of Methocel E4M 4000 cps in the proposed formulations with microcrystalline cellulose and glycerol ditripalmitostearate for hygroscopic and also for non-hydroscopic therapeutic agents. This combination is particularly advantageous for the preparation of sustained release systems of the present invention and in clinical tests it shows a bioavailability which is comparable with or superior to that of the known commercial preparations. No prior chemical or physical treatment of hydroxypropylmethylcellulose as proposed in some instances in the cited prior art is necessary for manufacturing the tablets of the present invention. Upon addition of the therapeutic agent and other ingredients, the mixture has an excellent compressibility and the tablets prepared therefrom are hard, stable and of low friability and provide a slow release rate of the therapeutic agent. The tableting of some therapeutic agents can be achieved by direct compressing without prior granulation, e.g. in the manufacture of aminophylline and propranolol hydrochloride sustained release tablets. For the manufacture of sustained release tablets of the present invention, various hygroscopic and non-hygroscopic therapeutic agents can be used, e.g. antiinflammatory substances (ketoprofen, indometacine, ibuprofen), coronary and cerebral vasodilators, peripheral vasodilators, anti-infectives, psychotropics and antimanics (lithium carbonate), antihistamines and anti-ulcus substances, laxatives, antiarrhythmics and anti-hypertensive drugs (propranolol hydrochloride), diuretics and drugs used in the treatment of migraine (dihydroergotamine mesylate) and many others.

It was found that sustained release tablets can be obtained by compressing high viscosity grade, i.e. high molecular weight hydroxypropylmethylcellulose (Methocel E4M, 4000 cps, Premium), microcrystalline cellulose, optionally glycerol ditripalmitostearate and other fillers, and the therapeutic agent in definite proportions. When the tablet is brought in contact with water or digestive fluids, a certain percentage of the therapeutic agent is rapidly released from the preparation into the solvent. The hydratation and the swelling of cellulose take place on the contact surface of the tablet with water and a gel barrier is formed. The rest of the therapeutic agent is then released more slowly, depending on the diffusion rate across the gel barrier and/or on its attrition.

The method for manufacturing sustained release tablets is based either on direct tableting or on previous dry or wet preparation of granules, which comprises thoroughly blending the hydroxypropylmethylcellulose carrier with the therapeutic agent in powdery or granular form, optionally with glycerol ditripalmitostearate and the remaining conventional adjuvants used in the tablet manufacture, e.g. magnesium stearate, lactose, starch, i.e. binding, filling and swelling agents etc. The ingredients are compressed in conventional tableting machines to give products of desired shape, weight, hardness and low friability, thus providing for the desired prolonged release of the therapeutic agent within a period of up to 12 hours, depending on the shape and the hardness of the tablets and particularly on the carrier. Thus it is possible to produce long-acting ot sustained release tablets in a relatively simple and economical manner.

The following illustrative Examples are not to be considered limitative.

Example 1

Sustained release 350 mg aminophylline tablets (retard tablets) containing 27.8 % Methocel E4M, 4000 cps, Premium, are prepared from untreated Methocel E4M.

The 350 mg aminophylline tablets are prepared from the following ingredients:

Ingredients	mg/tablet	%
Aminophylline anhydrous	350.0 mg	54.68
Microcrystalline cellulose (Avicel)	74.0 mg	11.56
Aerosil 200	6.5 mg	1.01
Precirol Ato 5 Gattefossé	18.0 mg	2.81
Magnesium stearate	5.5 mg	0.85
Dye FD & C 5 Yellow Al. lake	8.0 mg	1.25
Methocel E4M, Premium	ad 640.0 mg	27.8

Note:
Precirol Ato 5 (Gattefossé) is the commercial designation for glycerol ditripalmitostearate. Methocel E4M Premium is the designation of hydroxypropylmethylcellulose 4000 cps. Aerosil 200 is the designation for high purity SiO_2 (see H.P. Fiedler Lexikon der Holfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete; 2nd Edition 1981; Editio Cantor, Aulendorf, West Germany). The dye FD & C 5 Yellow Al. lake (Capsugel AG, Basel) is on the tartrazine basis.

The anhydrous aminophylline, Methocel E4M, the dye, a part of Precirol, Aerosil and magnesium stearate are passed through an appropriate sieve and after the mixing the mixture is shaped into briquettes. The briquettes are ground to the desired granulation. To the granulate the remaining microcrystalline cellulose (Avicel), Precirol and magnesium stearate are added and mixed. The thus obtained granulate is compressed to tablets of desired shape, weight and hardness, whereby an adequate release of the therapeutic agent is achieved.

Test Results

Stability

The results of the analyses of accelerated and current stability tests demonstrate that the solid drug unit dosage form of sustained release 350 mg aminophylline tablets on the hydroxypropylmethylcellulose, type Methocel E4M Premium, carrier base material meets the requirements with respect to both the therapeutic agent release from the tablet and the chemical and physical stability over the whole storage time, as it is evident from the following tables with test results.

Table 1

Storage time (months)	+Storage conditions				++Storage conditions			
	20±5°C	40±1°C	50±1°C	25°C 80% rel. humidity	20±5°C	40±1°C	50±1°C	25°C 80% rel. humidity
0	100.0%	-	-	-	100.0%	-	-	-
3	99.5%	99.2%	99.7%	-	100.0%	96.5%	95.0%	-
6	99.9%	99.7%	99.2%	96.1%	99.5%	95.3%	93.8%	95.9%
12	101.1%	98.9%	97.5%	-	98.1%	91.0%	86.7%	-
24	98.5%	-	-	96.7%	96.4%	-	-	96.2%
37	97.8%	-	-	95.8%	96.7%	-	-	95.8%

\+ Content: anhydrous theophylline; declared content = 300.0 mg (100 %)

++ Content: ethylene diamine; initial content = 52.22 mg (100 %)

Note: The results are expressed as a mean value of four determinations.

Hardness (N)

Apparatus: Erweka BT, producer Erweka-Apparatebau GmbH, Heuenstamm, Kr. Offenbach Main, West Germany

Table 2

Storage time (months)	Storage conditions 20 ± 5°C
0	53.9 - 78.4 N
3	53.9 - 78.4 N
6	58.8 - 78.4 N
12	53.9 - 88.2 N
37	44.1 - 78.4 N

The results are given for 10 tablets from minimum to maximum hardness.

Dissolution (release rate)

350 mg aminophylline tablets containing 300 mg of the therapeutic agent theophylline.
Storage conditions: blister - room temperature.
Apparatus: apparatus 3 (USP XX).
Medium: artificial gastric and intestinal fluids, 600 ml.
Temperature: 37°C.
Quantitative analysis: UV spectrophotometry, 275 nm.
Requirement: after 1 hour: 10-30 %
after 3.5 hours: 45-75 %
after 7 hours: 80 %

Table 3

Time (hrs)	% of released theophylline		
	analysis 1	analysis 2	analysis 3
1	15.7%	15.5%	15.2%
3.5	58.6%	54.3%	52.0%
7	89.0%	85.1%	84.0%

The foregoing tables demonstrate that even after prolonged storage at elevated temperatures sustained release aminophylline tablets remain practically unaltered, which assures a shelf life of 3 years at a temperature up to 25°C.

In vitro release rate of theophylline from sustained release 350 mg aminophylline tablets (A) of the aforesaid composition and from the commercial preparation sustained release 350 mg Phyllocontin® forte tablets (P)

Apparatus 3 (USP XX).
Medium: artificial gastric and intestinal fluids, free of enzymes (USP XXI), 600 ml.

Temperature: 37°C.
Quantitative analysis: UV spectrophotometry. 275 nm.

Time (h)	% of released theophylline ($\bar{X}$, n=6)	
	A	P
1	22.1	17.9
2	35.4	32.6
3.5	58.5	59.4
5	75.0	79.7
7	85.9	93.4

Sustained release 350 mg Aminophylline tablets (A)

	C_{max} (μg/ml)	t_{max} (h)	AUC^{0-24} (μg.h/ml)	$AUC^{0-\infty}$ (μg.h/ml)
mean	4.925	4.4	73.42	116.09
range	3.536-6.735	3-6	49.57-103.50	72.21-164.89
No. of s.	10	10	10	10

Sustained release 350 mg Phyllocontin forte tablets (P)

	C_{max} (μg/ml)	t_{max} (h)	AUC^{0-24} (μg.h/ml)	$AUC^{0-\infty}$ (μg.h/ml)
mean	4.301	5.3	68.75	100.64
range	3.076-6.559	2-8	41.58-122.70	55.19 - 187.52
No. of s.	10	10	10	10

Note:
C_{max} = maximal concentration of therapeutic agent in blood
t_{max} = time to maximal concentration of therapeutic agent in blood
AUC = area under the plasma concentration of therapeutic agent curve
No. of s. = number of subjects

The comparison preparation for sustained release 350 mg aminophylline tablets was the commercial preparation sustained release 350 mg Phyllocontin® forte tablets. The plasma concentration curve has a form suitable for a sustained release formulation. The pharmacokinetic parameters do not differ statistically significantly.

Example 2

Sustained release 150 mg ketoprofen tablets containing 25.9 % Methocel E4M, Premium, 4000 cps, are prepared from untreated Methocel E4M.

The tablets are prepared from the following ingredients:

Ingredients	mg/tablet	%
Ketoprofen	150.0 mg	51.72
Methocel E4M, 4000 cps, Premium	65.0 mg	22.41
microcrystalline cellulose (Avicel)	62.5 mg	21.55
magnesium stearate	3.0 mg	1.03
Aerosil 200	2.0 mg	0.68
polyvinylpyrrolidone K 25	7.5 mg	2.58

Ketoprofen and microcrystalline cellulose (Avicel) are mixed and then passed through an appropriate sieve. A part of Aerosil and of magnesium stearate are added to the mixture, which is then granulated with polyvinylpyrrolidone K 25. The granules are dried, passed through an appropriate sieve, then Methocel E4M Premium, the remaining Aerosil and magnesium stearate are added and mixed. The obtained granulate is tableted to tablets of desired shape, weight and hardness, whereby an appropriate release of the active ingredient is achieved.

Test results

Stability

Table 1: Ketoprofen content

Initial content: 149.7 mg/tablet = 100.0 %

Storage time (days)	Storage conditions $4\pm1^{\circ}C$	$20\pm5^{\circ}C$	$30\pm1^{\circ}C$	$40\pm1^{\circ}C$	$50\pm1^{\circ}C$ 80%	$25\pm1^{\circ}C$
92	101.1%	100.9%	100.0%	97.9%	94.4%	98.7%
186	100.9%	99.2%	98.3%	98.6%	95.9%	99.3%
356	100.4%	98.8%	99.7%	99.8%	-	99.8%

Table 2: Hardness of the tablets (N)

Apparatus: Erweka BT

Initial value: 34.3-78.4 N

Storage time (days)	Storage conditions $4^{\circ} \pm 1^{\circ}C$	$20^{\circ} \pm 5^{\circ}C$	$30^{\circ} \pm 1^{\circ}C$
92	34.3 - 44.1	44.1 - 58.8	53.9 - 63.7
186	39.2 - 53.9	39.2 - 53.9	58.8 - 68.6
356	53.9 - 63.7	49.0 - 63.7	58.8 - 68.6

Table 3: Dissolution test (release rate)

Sustained release 150 mg ketoprofen tablets
Storage conditions: small bottle - room temperature
Apparatus 1 (USP XXI): 100 rpm
Medium: artificial gastric and intestinal fluids, 1000 ml
Temperature: 37°C
Quantitative analysis: UV spectrophotometry, 258 nm
Requirement: after 1 hour: 10-30 %
after 4 hours: 30-60 %
after 8 hours: 50-75 %
after 12 hours: > 70 %

Time (hrs)	% of released ketoprofen		
	analysis 1	analysis 2	analysis 3
1	21.6	21.3	20.7
4	54.1	53.1	52.8
8	73.4	71.2	72.5

On the basis of the accelerated stability test results it can be concluded that sustained release 150 mg ketoprofen tablets are stable and that at the temperature of up to 25°C there can be assumed a shelf life of 5 years.

In vitro dissolution or release rate of ketoprofen from tablets (50.0 mg) and from sustained release 150 mg ketoprofen tablets with aforesaid composition.

Apparatus 1 (USP XXI): 100 rpm
Medium: phosphate buffer, pH 5.7, 900 ml
Temperature: 37°C
Quantitative analysis: UV spectrophotometry, 258 nm

Time (min)	% of ketoprofen released from tablets (n=6)
5	59.6
15	91.6
30	96.5

Apparatus 1 (USP XXI): 100 rpm
Medium: artificial gastric and intestinal fluid, free of enzymes (USP XXI), 1000 ml
Temperature: 37°C
Quantitative analysis: UV spectrophotometry, 258 nm

Time (hrs)	% of ketoprofen released from sustained release ketoprofen tablets (n=6)
1	19.1
4	48.8
8	63.7
12	76.5

Samples of sustained release 150 mg ketoprofen tablets were tested in vivo in humans and compared with two 50 mg ketoprofen tablets after a single application. The results are given in the following table:

Type of tablets	Time to maximal concentration (hrs)	Maximal concentration (mg/l)	Total area under the curve (mg.h/l)
Sustained release 150 mg tablets			
mean	5.44	2.31	26.1
range	(2.0-12.0)	(1.39-3.49)	(15.5-42.3)
No. of subjects	9	9	9
Conventional tablets 2 x 50 mg			
mean	1.48	9.65	21.20
range	(0.67-3.00)	(6.30-15.20)	(17.27-30.99)
No. of subjects	8	8	8

The table clearly demonstrates the influence of prolonged release from the sustained release form upon the ketoprofen pharmacokinetics, which allows the number of application to be reduced to 1-2 daily.

Example 3

Sustained release 160 mg propranolol hydrochloride tablets containing 36.2 % Methocel E4M Premium, 4000 cps, are prepared from untreated Methocel E4M. The tablets are prepared from the following ingredients:

Ingredients	mg/tablet	%
Propranolol hydrochloride	160	46.38
Methocel E4M, 4000 cps, Premium	125	36.23
microcrystalline cellulose	45.2	13.10
Precirol ATO 5	9.9	2.87
Aerosil 200	3.3	0.96
magnesium stearate	1.6	0.46

Sustained release propranolol tablets were prepared by briquetting the ingredients, followed by domminuting the briquettes, sieving throuhg an appropriate size sieve and forming a granulate.

The resulting granulate is homogenously mixed under the addition of an appropriate lubricant and again passed through a sieve.

The thus obtained granulate is tableted to tablets of desired shape, weight and hardness, whereby an appropriate release of the therapeutic agent is achieved.

Test results

Stability

Table 1: Propranolol hydrochloride content

Initial content: 160 mg propranolol hydrochloride per tablet = 100.0 %

Storage time (days)	Storage conditions					
	4±1°C	20±5°C	30±1°C	40±1°C	50±1°C	80 % humidity (25°C)
126	99.1%	100.6%	99.8%	100.0%	99.9%	99.7%
220	100.7%	99.0%	100.7%	100.3%	100.8%	100.2%
380	99.5%	100.0%	99.3%	99.0%	100.0%	99.6%

Table 2: Hardness of the tablets (N)

Apparatus: Erweka BT
Initial value: 39.2 - 68.6 N

Storage time (days)	Storage conditions		
	4° ± 1°C	20° ± 5°C	30° ± 1°C
126	58.8 - 68.6	63.7 - 68.6	63.7 - 73.5
220	49.0 - 63.7	44.1 - 73.5	58.8 - 73.5
380	73.5 - 88.2	73.5 - 88.2	78.4 - 88.2

Table 3: Dissolution test (release rate)

Propranolol hydrochloride: 160 mg tablets
Storage conditions: blister - room temperature
Apparatus 3 (USP XX)
Medium: artificial gastric fluid and intestinal fluids free of enzymes (USP XXI), 600 ml
Temperature: 37°C
Quantitative analysis: UV spectrophotometry, 286 nm
Requirement: after 1 hour: 10-30 %
after 4 hours: 40-75 %
after 8 hours: > 75 %

Time (hrs)	% of released propranolol hydrochloride				
	analysis 1	analysis 2	analysis 3	analysis 4	analysis 5
1	26.8	22.0	22.5	22.8	22.5
2	41.4	35.4	37.0	37.2	35.9
4	62.9	56.3	56.5	57.7	56.0
6	78.2	73.1	70.6	74.1	71.8
8	88.8	83.4	81.1	83.7	84.0

On the basis of accelerated stability test results it was found that sustained release 160 mg propranolol hydrochloride tablets are stable and at at the temperature of 25°C a shelf life of 3 years can be assured.

In vitro release rate of propranolol hydrochloride from sustained release 160 mg tablets with aforesaid composition (P) and form the commercial preparation sustained release 160 mg Inderal® tablets (I).

Apparatus 3 (USP XX)

Medium: artificial gastric and intestinal fluids free of enzymes (USP XXI), 600 ml

Temperature: 37°C

Quantitative analysis: UV spectrophotometry, 286 nm

Time (hrs)	% of released propranolol hydrochloride	
	P	I
1	19.5	17.0
2	31.8	35.2
4	50.3	56.2
6	65.5	69.0
8	77.3	77.4

Sustained release 160 mg propranolol hydrochloride tablets

	t_{max} (h)	C_{max} (ng/ml)	AUC^{0-24} (ng.h/ml)	$AUC^{0-\infty}$ (ng.h/ml)
mean	5.0	22.09	292.29	492.92
range	2.0-13.8	11.10-41.50	134.68-727.70	194.64-1695.31
No. of s.	8	8	8	8

Sustained release 160 mg Inderal^{R} tablets

	C_{max} (ng/ml)	t_{max} (h)	AUC^{0-24} (ng.h/ml)	$AUC^{0-\infty}$ (ng.h/ml)
mean	16.64	6.75	20.60	389.71
range	4.30-25.40	5-12	73.10-383.23	163.74-1376.28
No. of s.	8	8	8	8

Note:
C_{max} = maximal concentration of therapeutic agent in blood
t_{max} = time to maximal concentration of therapeutic agent in blood
AUC = area under the plasma concentration of therapeutic agent curve
No. of s. = number of subjects

The comparison preparation for sustained release 160 mg propranolol hydrochloride tablets were sustained release 160 mg Inderal® tablets. The above results demonstrate the superior bioavailability of sustained release propranolol tablets (approximately 25 %, as calculated from $AUC^{0-\infty}$) . The plasma concentration diagrams are suitable for a sustained release form.

Claims

1. Sustained release tablets comprising a therapeutic active agent and a carrier base material, characterized in that the carrier base material comprises hydroxypropylmethylcellulose having a methoxyl content of 28 to 30 weight-%, a hydroxypropoxyl content of 7.5 to 12 weight-% and an average molecular weight of at least 50 000, in a proportion of about 20 to about 40 weight-% of the tablet, optionally up to 10 weight-% of glycerol ditripalmitostearate and from about 10 to about 20 weight-% of microcrystalline cellulose and other conventional pharmaceutically acceptable adjuvants.

2. Sustained release tablets as claimed in claim 1, characterized in that the therapeutic agent is selected from, yet not limited to aminophylline, theophylline, ketoprofen, propranolol hydrochloride, dihydroergotamine and other ergot alkaloids in the form of acid addition salts, glyceryl trinitrate, isosorbide dinitrate and lithium carbonate.

3. A process for the manufacture of sustained release tablets as claimed in claim 1, characterized in that a mixture of a therapeutic agent and a carrier base material, comprising hydroxypropylmethylcellulose having a methoxyl content of 28 to 30 weight-%, a hydroxypropoxyl content of 7.5 to 12 weight-% and an average molecular weight of at least 50 000 in a proportion of about 20 to about 40 weight-% of the tablet, optionally up to 10 weight-% of glycerol ditripalmitostearate and from about 10 to about 20 weight-% of microcrystalline cellulose and other conventional pharmaceutically acceptable adjuvants, is compressed and shaped.

4. A process for the manufacture of sustained release tablets as claimed in claim 3, characterized in that the therapeutic agent is selected from, yet not limited to aminophylline, theophylline, ketoprofen, propranolol hydrochloride, dihydroergotamine and other ergot alkaloids in the form of acid addition salts, glyceryl trinitrate, isosorbide dinitrate and lithium carbonate.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 10 3715

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
P,X	GB-A-2 181 053 (SANDOZ LTD) * Page 2, line 8 - page 3, line 46; examples 17,20 *	1,3	A 61 K 9/22 A 61 K 9/26
Y	GB-A-2 170 407 (SANDOZ LTD) * Page 1, line 1 - page 3, line 55 *	1-4	
Y	EP-A-0 156 592 (AMERICAN HOME PRODUCTS CORP.) * Page 5, line 3 - page 6, line 26 *	1-4	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	27-06-1988	TZSCHOPPE, D.A.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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